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The Superhero Drugs for Choroidal Neovascularization; Anti-VEGF Agents

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A decade ago, the treatment of choroidal neovascularization (CNV) secondary to various macular diseases like age related macular degeneration, pathologic myopia, and angioid streaks was a crucial challenge. Laser photocoagulation could might be performed for juxtafoveal and extrafoveal CNVs and different surgical treatment options like macular translocation surgery and subretinal CNV excision were available. The published studies usually were about neovascular age-related macular degeneration (nAMD), and we tried to adapt them to the other causes of CNV. However, the outcomes of these treatment options were variable and far away from patient and physician satisfaction [1].

In early 2000s, photodynamic therapy (PDT) was introduced and for the first time we could treat the subfoveal lesions with a non-surgical method; however, again the treatment outcomes were mostly about the patients who lost less than 3 LogMAR lines [1] After the intravenous administration of Verteporfin, a photoactive agent; non-thermal diode laser was applied to the CNV. PDT was satisfactory enough for preserving visual acuity; however, visual acuity increases could have been achieved only in a very low portion of the patients. Also, lately many of the patients developed chorioretinal atrophy areas corresponding to the previous PDT spots. Then the intravitreal anti-vascular endothelial growth factor agents came with better visual results [1]. The first anti-VEGF drug used and licensed to treat CNV secondary to nAMD was pegaptanib Pegaptanib[1]. It was an aptamer of VEGF A-165 receptor isoform, and selectively targeted the mentioned receptor of VEGF [1]. First results were promising, but pegaptanib could not achieve the visual results of the following drugs which were antibodies against all isoforms of VEGF-A; the off label one bevacizumab, and on label one ranibizumab [1]. The first results of single center, non-randomized studies concerning about intravitreal bevacizumab treatment in nAMD were very satisfactory and we began to talk about visual acuity gains. Then in 2005 ranibizumab was introduced which was the rhuFab fragment of the monoclonal antibody against all isoforms of VEGF-A. Many studies were published about the efficacy of ranibizumab in the treatment of CNV secondary to various diseases. The monthly, quarterly, as-needed treatment regimens were evaluated in the studies such as MARINA, ANCHOR, EXCITE, PRONTO [1].

After these studies, monthly and especially as-needed treatment regimens have become very popular. Lately, new flexible treatment regimens were introduced like treat and extend which carried the advantage of both of the previous treatment regimens, with less visit number than the former, more visit numbers than the latter. In late 2000s and early 2010s, the efficacy and safety profile of bevacizumab and ranibizumab were questioned frequently. Several single center, prospective and retrospective studies were carried out to solve this problem. Many of them showed that the two drugs seemed equal to each other in both safety and efficacy parameters. In 2011 a multicenter, randomized, non-inferiority trial gave the most correct answer. In the CATT trial, it was reported that bevacizumab was non-inferior to ranibizumab in terms of visual results. However, safety issues were not clearly elucidated in this study [2].

While the debate about the two drugs was ongoing a new actor came into sight in 2011. Aflibercept, which is a recombinant fusion protein and acts on the VEGF A-B-C and placental growth factor were approved by US Food and Drug Admininistration. Aflibercept was showed to be non inferior to ranibizumab in terms of visual and anatomic results with less number of injections [3]. Also according to some new studies aflibercept seems to be effective in some of the ranibizumab and bevacizumab non-responder patients. This phenomenon may be attributed to the mechanism of action of aflibercept; because it interferes with all subtypes of VEGF receptors including placental growth factor as mentioned before. However, it is speculated that this advantage may be a disadvantage in terms of systemic side effects. Until now there some safety results regarding ranibizumab and aflibercept were published, but similar to the situation with bevacizumab, this questions remains unanswered nowadays.

We have just three drugs in the market in these days which are similar to each other in terms of treatment outcomes. It seems that in the following five or ten years the anti-VEGF drugs will continue to be the main treatment option in CNV secondary to various macular diseases and there are several agents in the pipeline [1,3]. Different agents that attack the different parts of the VEGF cascade and novel delivery systems are being evaluated in several trials. Integrin blockers, conbercept, designed ankyrin repeating proteins (DARPins), anti-PDGF agents, hypoxia-inducible factor 1-α inhibitors, tyrosine kinase inhibitors, combretastatin, sonepcizumab are some of the new drugs which are being evaluated [1,3]. Also novel delivery systems like

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sustained-releases, refillable reservoirs, and suprachoroidal delivery are being investigated [1,3].

As a conclusion, two decades ago, we were desperately inevitable in the treatment of CNV secondary to macular diseases; a decade ago, we became visual protectors; finally thank to anti-VEGF agents that we now may save the visual acuity in most of the CNV patients and may obtain significant visual acuity gains in nearly half of the CNV patients.

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